

Spirochetes in Late Seronegative Syphilis, Penicillin Notwithstanding. By J. LAWTON SMITH, M.D. 1969. Pp. 343, illus. Thomas Springfield, Ill. (\$36)

The sensational nature of the title of this book is belied by a careful reading of the text; what is well documented is not new, what seems to be new is not proved. The book is written with a flair which holds one's interest, but often obscures the lack of definitive evidence.

Of the 37 chapters, seven comprise two pages or less. The author has collaborators for five chapters, and one is by Dr. Charles W. Israel alone. The first five chapters constitute a useful review of the clinical signs and pathology of ocular and neurosyphilis. There follows a succession of some three score case reports, with comments, supporting the thesis that many patients with physical evidence of late ocular or neurosyphilis show negative or equivocal results when tested with the customary lipoidal-antigen tests for syphilis. While this has been well recognized for years, it is a service to emphasize the fact anew, and to call attention to the desirability of using the TPI and FTA tests as diagnostic aids. Of the first 64 cases presented in the main clinical section of the book there was evidence of previous penicillin treatment in only nine, and in some of these documentation was fragmentary. Moreover, it was difficult to be sure that the physical and serological findings in many instances did not represent the end stages of a largely inactive syphilitic process.

The greatest interest attaches to the search for treponemal forms in the aqueous humour and cerebrospinal fluid in patients with late syphilis. Although such organisms have been demonstrated in both aqueous humour and cerebrospinal fluid from time to time over many years (most recently for aqueous humour, by Agarwal, 1960, in Amsler's Clinic), it is perhaps Smith's greatest contribution that he has re-emphasized and stimulated new interest in this phenomenon, especially in late syphilis. That the true nature of these treponeme-like organisms in most instances is not clear does not minimize the importance of the finding, and certainly adds zest to further research. The author unfortunately is misled by over-confidence in the specificity of the fluorescent antibody test as usually performed, into assuming that the spirochaetes observed microscopically are in fact *T. pallidum*.

He has properly turned to laboratory animals as one method by which pathogenic *T. pallidum* can be reasonably definitively identified. But largely ignoring methods used by experimental syphilologists for many years, he has approached the problem in such novel fashion that one is left with considerable question in

most instances whether syphilitic infection has been established in the animal or not. For example, simple darkfield demonstration of active treponemes in the test animal has not been accomplished in most instances. Great store is set by the value of alopecia in the rabbit as a sign of syphilitic infection, but this reviewer has never seen a type of alopecia in syphilitic rabbits that does not also occur in non-syphilitic rabbits. Again, the author has used small primates, owl and squirrel monkeys, as test animals when his own results suggest that these animals react relatively mildly to the infection. In both rabbits and monkeys he has regarded an occasional positive serological test as evidence of syphilitic infection, a most unreliable guide indeed.

When all this has been said, however, it must be noted that Smith's work has stimulated other investigators, and as the results come in the parameters of the problem may be more easily identified. Pathogenic *T. pallidum* can certainly be found at times in both aqueous humour and spinal fluid in late syphilis, and evidence is beginning to accumulate that these might occur in the face of recent penicillin therapy, but there is no indication whatever that this is a frequent occurrence. As interesting perhaps is the question that arises in many cases: if these are not true *T. pallidum* what are they, and what is their significance, if any, in terms of human disease?

Enthusiasms have their role in medicine and science, as long as those enthusiasms are tempered by the accumulation of objective data which can be tested and retested by like-minded investigators. It is to be hoped that many other investigators will be stimulated to study the two problems to which Smith has dramatically called attention in this book, seronegativity in the presence of recognizable lesions of syphilis, such as tabes and optic atrophy; and the significance of the presence of treponeme-like microorganisms in the aqueous humour and cerebrospinal fluid in such cases.

Thomas B. Turner

It has long been customary to speak of "cure" in late syphilis with some caution, the more so since the initial reports by Collart and his colleagues of the finding of treponemes in material from patients and animals after apparently adequate treatment with penicillin. The author has contributed largely to the recent literature in this field. He is fortunate in working in an area where late syphilis is still plentiful, some 700 such cases having been found at this hospital over a 4-year period. From these, 200 cases were selected for presentation in this monograph. Its

title needs some clarification; "sero-negative" refers to results with tests for anti-lipoidal antibody, while specific treponemal tests, such as the TPI or FTA-ABS, may give positive results. His main theme is that treponemes may be found in material from patients with clinical manifestations of late syphilis even after treatment with penicillin and even though serological tests, including sometimes specific treponemal tests, give negative results; clinical judgment should not be overawed by negative serological findings.

The clinical aspects and classifications of ocular and neurosyphilis are reviewed and illustrated by numerous case reports. Chapters on the laboratory aspects deal with the demonstration of treponemes by fluorescent antibody and silver-staining techniques and on the FTA-ABS test; this is thought to be the most useful means of detecting late syphilis. The application of these methods in the study of experimentally produced infection in rabbits and monkeys is described.

The most instructive part of the book is devoted to case histories of patients, some of whom had been treated, in whose aqueous humour or spinal fluid treponemes were found, and on the results of infectivity tests. The author thinks these treponemes to be *Treponema pallidum*, although he honestly admits to having been misled by artefacts in a few cases. From the mode of presentation, which cites only positive findings, it is difficult to see the wood for the trees. It is stated (p. 250) that the cases presented "were selected from over 300 patients studied with the fluorescent antibody tissue stain in which the organisms have been documented"—presumably, that is, found. From p. 225 it seems that over 2,000 patients have been studied. What is lacking is any analysis of the material as a whole, so that the incidence of positive findings in the various clinical categories of late syphilis can be judged. This omission detracts greatly from the value of the presentation.

Some of the serological terms used are unusual. Tests are referred to as "false negatives" when they give a negative result in a patient with syphilis; a "pseudo-B.F.P. reaction" indicates a positive test for reagin but a negative TPI test in the presence of late syphilis. These seem to carry the implication that

tests ought regularly to be positive in the presence of syphilis; if only they were, syphilis serology would be much simpler than it is.

The author has made extensive use of the fluorescent antibody method for the detection of *T. pallidum*. Yet, in the chapter on the technique used, no mention is made of the necessity to control the specificity of the reagents used to demonstrate *T. pallidum* as distinct from other treponemes. In the indirect technique recommended, high-titred serum from a case of secondary syphilis is diluted 1 in 5 in the sorbent used for the FTA-ABS test. Whether such treatment is sufficient to remove all group-reactive antitreponemal activity from such a serum is questionable, and this reagent should be checked to ensure that it does not react with other treponemes as well as with *T. pallidum*. The only unquestionable evidence for the identification of *T. pallidum* is a positive infectivity test with the production of a lesion containing treponemes in an experimental animal. Four of the cases in which animals were inoculated with material from patients with late syphilis meet this requirement; in others, the development of positive specific treponemal tests gave indirect evidence suggesting that infection has occurred.

Despite these criticisms, the author has done a most useful service in presenting his results. Syphilis has rightly been called the great imitator; perusal of these very full case histories could do much to foster a higher level of suspicion among physicians; without this, it is certain that many cases of late syphilis will remain unsuspected and so undiagnosed. That microbial persistence may occur in syphilis despite treatment is now established. How frequently it occurs is not known, nor is its significance for the individual patient, nor what alterations in treatment may be called for. It is to be hoped that the information in this book will stimulate others to enter this field of investigation.

The book is very well produced and lavishly illustrated. Magnification of photomicrographs is seldom given and hence the treponemes depicted appear to vary very considerably in size. Unfortunately the price will deter most people but the book should find a place in departmental libraries.

A. E. Wilkinson